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Postpartum Fatigue and Evidence-Based Interventions

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ABSTRACT

The aim of this article is to review postpartum fatigue, especially as it relates to the occurrence and pathophysiology of three common postpartum conditions known to contribute to fatigue: anemia, infection/inflammation, and thyroid dysfunction. Fatigue is an unrelenting condition that affects physical and mental health, and it has implications for everyday activities, motivation, and social interactions. Although individuals of all ages and both genders are at risk for developing fatigue, postpartum fatigue is particularly challenging, because the new mother has demanding life tasks to accomplish during this period of time. Postpartum fatigue may impact postpartum maternal role attainment and may place a woman at increased risk for postpartum depression. Although several treatable physiological conditions common during the postpartum period are known to increase fatigue, none of these conditions is a part of the usual assessment of healthy postpartum women. For many women, subtle fatigue may develop, linger or worsen, and even lead to depression, with both the woman and her care provider unaware.

Key Words: Postpartum fatigue; Anemia; Hypothyroid; Inflammation; Postpartum depression; Evidence-based practice.

Postpartum fatigue is a debilitating condition that may have an impact on a new mother's ability to care for her child (Troy, 2003). It also may delay a woman's return to functional status in the areas of household, social, employment, and self-care responsibilities (Troy, 2003; McQueen & Mander, 2003) and increase her risk of postpartum depression (PPD) (Corwin, Brownstead, Barton, Heckard, & Morin, 2005). Although fatigue likely exists on a continuum, the percentage of women who identify fatigue as a significant symptom is estimated to increase from 20% preconceptionally to 50% to 64% among women immediately postpartum (Lee & Zaffke, 1999). In one of the first studies about this topic, Affonso, Lovett, Paul, and Sheptak (1990) reported that nearly 70% of the women in their study acknowledged elevated fatigue 1 to 2 weeks postpartum compared to nonpregnant women, with 40% continuing to report elevated levels 12 weeks later. For many women, lingering fatigue is a serious problem. In one study, among a sample of 436 mothers, 44% rated postpartum fatigue as their second most frequent complaint (to breast problems) at 1 month postpartum; at 3 and 6 months postpartum, fatigue was the third most frequent complaint (after respiratory and sexual problems) (Gjerdingen, Froberg, Chaloner, & McGovern, 1993).

Three Common Contributors to Postpartum Fatigue

Postpartum fatigue is often seen as an inevitable consequence of the transition to motherhood. Although it is true that situational factors, such as 24-hour infant care and caring for other children in the home, may contribute to fatigue (McQueen & Mander, 2003), physical conditions that increase postpartum fatigue also exist. These conditions include anemia, infection/inflammation, and thyroid dysfunction, all of which are amenable to evidence-based interventions.

Anemia

Anemia is defined as a hemoglobin (Hb) concentration less than the established cutoff delineated by the World Health Organization (WHO) for a particular population. The latest WHO report on anemia in pregnancy (WHO, 1992) estimates that 43% of nonpregnant women of reproductive age in developing countries, and 12% in industrialized countries, are anemic; these estimates rise to 56% and 18%, respectively, by the third trimester of pregnancy. After childbirth, Hb levels fall slightly during the first 24 hours because of blood loss and then rise over the next 2 to 5 days. Hb should return to the normal nonpregnant range by 7 days (Milman, 2006).

In Western countries, the most common cause of anemia during pregnancy and the postpartum period is iron deficiency. Daily iron demand increases nearly 10-fold from the start of a pregnancy to term (Milman, 2006). However, less than 25% of women start their pregnancies with iron stores sufficient to meet requirements, and only 5% increase their iron intake sufficiently during pregnancy to make up that difference (Milman, 2006). This means that even with iron supplementation, by term a large number of pregnant women are iron depleted, if not frankly anemic. Full compliance with iron recommendations during pregnancy is rare, with less than 30% of women fully compliant and an equal percentage denying any iron supplementation during pregnancy (Nordeng, Eskild, Nesheim, Aursnes, & Jacobsen, 2003).

During the postpartum period, iron deficiency continues or worsens for a significant percentage of women. Milman, Bergholt, Keld-Erik, Eriksen, and Graudal (1999) found that 8 weeks after an uncomplicated delivery, 16% of women not receiving supplemental iron during pregnancy were iron deficient, and 12% had frank iron deficiency anemia. Of women who used iron supplementation consistently during pregnancy (66 mg daily), 3% were iron deficient and 1.6% were anemic. In a study of low-income women, Bodnar, Cogswell, and Scanlon (2002) reported postpartum iron deficiency prevalence rates of 12.7%, 12.4%, and 7.8% at 0 to 6, 7 to 12, and 13 to 24 months postpartum, respectively. Postpartum women in the lowest income group (poverty index ratio <130%) were four times more likely to be anemic at 0 to 6 months and three times more likely to be anemic at 6 to 12 months postpartum, compared to more affluent women.

> Iron deficiency anemia is common during pregnancy and the postpartum period, especially in young and low-income women, and is linked to postpartum fatigue and poor health outcome.

Iron deficiency anemia is linked to postpartum fatigue and other poor health outcomes. In one study, women with low Hb levels (<12 g/dL) at 3 months postpartum were more likely to have postpartum fatigue (Lee & Zaffke, 1999). Besides fatigue, anemia is associated with irritability, apathy, and an inability to concentrate. Interestingly, Beck and Indman (2005) identified each of these factors as common presentations of PPD. Treatment of iron deficiency anemia in the postpartum period is straightforward but first requires diagnosis. Currently, the Centers for Disease Control and Prevention (CDC, 1998) recommend anemia screening at 4 to 6 weeks postpartum only for women who were diagnosed as anemic in the third trimester, who had experienced excessive blood loss during delivery, or whose pregnancies had resulted in a multiple birth. Other women are generally not tested for anemia after discharge unless they are symptomatic. Symptoms of iron deficiency anemia, however, are of-

Postpartum infection and postpartum thyroid deficiency may go undetected and contribute to lingering fatigue.

ten subtle, especially if the anemia has developed over a prolonged period. Even women who suffer excessive blood loss during or after delivery and are known to be severely anemic (Hb <9 mg/L), are typically sent home only with instructions to take iron. In a search of standard postpartum guidelines, we were unable to identify anticipatory guidance recommendations regarding the high level of fatigue these women should expect to experience (CDC, 1998).

Evidence-Based Intervention for Anemia

A clear, evidence-based intervention would be to identify, via a nurse-initiated telephone call, women who—when asked—report that they are experiencing a high level of postpartum fatigue. In our previous work, we have identified a score of >6 on a well-validated postpartum fatigue screening tool, the Modified Fatigue Symptom Checklist (Pugh, Milligan, Parks, Lenz, & Kitzman, 1999), administered on day 14 postpartum as above the normal range and indicative of severe postpartum fatigue (Corwin et al., 2005). Using this or a different tool or simply asking questions, screening for significant fatigue could be accomplished in a few minutes. Any woman who complains of severe fatigue at 2 weeks postpartum should be scheduled for an appointment, at which time she should be screened for anemia by obtaining (at a minimum) a test of Hb concentration or hematocrit. If the woman is not otherwise ill, a low Hb or hematocrit would allow for a presumptive diagnosis of iron deficiency anemia, and treatment could be initiated. All other postpartum women could be tested in the same manner for anemia at the 6-week postpartum visit. Treatment for anyone found to be anemic should include dietary advice regarding increased consumption of foods rich in iron, iron therapy, and anticipatory guidance regarding managing fatigue. Iron therapy involves iron administered orally at a dose between 60 and 120 mg/day (in divided doses) for at least 6 months (CDC, 1998). Follow-up laboratory analyses are required to evaluate treatment success. An increase in reticulocytes should be detectible within 7 to 10 days after initiation of oral iron therapy. Hb levels should begin to rise within 3 days, showing a maximum response by 4 weeks. An increase in Hb concentration of >1 g/dL or in hematocrit of >3% at 4 weeks confirms the diagnosis of iron deficiency anemia. With treatment, postpartum iron deficiency anemia should resolve within 12 weeks. Women who do not respond to iron therapy by 4 weeks should be evaluated for other causes of anemia.

Infection/Inflammation

Postpartum infection includes infections that occur in the first days after delivery (e.g., postpartum endometritis) and infections that may develop weeks after delivery (e.g., infectious mastitis). As with most infections, postpartum infections activate the immune system, resulting in inflammation and the production of proinflammatory cytokines. The exact incidence of postpartum infection is difficult to ascertain because most infections occur after hospital discharge. In one large study that included screening ambulatory medical records, emergency room reports, and pharmacy records of more than 2,800 women within 1 month of giving birth, the postpartum infection rate was 6%, with rates varying from 5.5% after vaginal delivery to 7.4% after cesarean section (Yokoe et al., 2001). The most common types of postpartum infection are endometritis, urinary tract infection, and mastitis (Yokoe et al., 2001). Other common sites include the vagina, vulva, perineum, and cervix. Obstetrical history regarding type of delivery, length of labor after rupture of membranes, internal fetal monitoring, manual removal of the placenta, catheterization during labor, and breastfeeding highlights women at greatest risk. Risk of infection is also increased for women with diabetes, HIV, or other immune deficiencies (Lehtovirta et al., 2005) and for obese women (Usha Kiran, Hemmadi, Bethel, & Evans, 2005). Infection can be diagnosed based on physical findings, including fever, foul-smelling vaginal discharge, pain on urination, and tenderness of uterus, abdomen, or breasts. Laboratory screenings include wound, cervical, breast milk, and urinary cultures.

Proinflammatory cytokines drive and mediate the immune response and are known to cause systemic symptoms, including fatigue. Although endometritis and mastitis often present with other more severe symptoms, including fever and pain, some infections (including urinary tract infection [UTI] and subclinical mastitis) may present with fatigue as the primary complaint in postpartum women. Postpartum women are susceptible to UTI for several months because of persistent postpartum ureteral dilation and vesicoureteral reflux. Likewise, mastitis may develop at any time in a woman who is breastfeeding.

Currently, there are no studies correlating either subclinical or frank infection and postpartum fatigue. Groer et al. (2005) did identify a relationship between postpartum fatigue and self-report of respiratory infection, although participants' report of infection was not objectively confirmed. Common sites for postpartum infection, such as the breasts, uterus, vagina, vulva, perineum, or cervix, were not specifically addressed by the researchers. Focusing on inflammation and fatigue in the postpartum period, however, previous work from our laboratory found that postpartum fatigue was positively correlated with increased urinary interleukin-1 beta in healthy women (Corwin, Bozoky, Pugh, & Johnston, 2003). In this study, none of the women were known or suspected to be suffering from an infection, however, and no cultures were performed.

Evidence-Based Intervention for Infection/Inflammation

Given the frequent occurrence of infection in the postpartum

period and the established association between infection, inflammation, and fatigue, a second evidenced-based intervention to reduce postpartum fatigue would be to evaluate all women for infection at the 6-week postpartum visit. This assessment should be done with the caveat that two groups of women should be screened earlier than 6 weeks: women at high risk for postpartum infection because of obstetrical or other factors and any woman scoring as significantly fatigued over the phone at 2 weeks postpartum. In addition to obtaining an accurate history and completing a focused physical exam at the 6-week visit, obtaining a urine culture and complete blood count with differential may identify women with infection. Anticipatory guidance for all women after childbirth that alerts them to subtle symptoms of infection (including symptoms that may develop months later) is another important intervention. Treatment would include the appropriate antibiotic therapy and a follow-up appointment to test for cure. Certain antibiotics, including the sulfonamides and quinolones, should be avoided in women breastfeeding their infants. Antibiotic prophylaxis for all women after cesarean section is recommended (Smaill & Hofmeyr, 2002).

Thyroid Dysfunction

The thyroid gland produces the hormones thyroxine (T4) and tri-iodothyronine (T3) in response to thyroid-stimulating hormone (TSH) released from the anterior pituitary gland. TSH in turn, is produced in response to stimulation by the hypothalamic hormone, thyrotropin releasing hormone (TRH), which is itself secreted in response to multiple metabolic signals. In healthy individuals, negative feedback among all thyroid hormones ensures that serum levels of TRH, TSH, T3, and T4 remain within a narrow range. Women with clinical hypothyroidism demonstrate elevated serum TSH levels in conjunction with reduced T4 (and to a lesser extent, T3); patients with subclinical hypothyroidism demonstrate elevated TSH levels in conjunction with normal levels of T4 (American Association of Clinical Endocrinologists [AACE], 2002). Total or free T3 levels are not considered diagnostic for hypothyroidism.

Most women without pre-existing hypothyroidism remain euthyroid during pregnancy, although de novo development of hypothyroidism during pregnancy does occur at an incidence rate of approximately 2.5% (Lazarus, 2003). After giving birth, between 1.1% and 16.7% (mean prevalence 7.5%) of previously well women develop a condition called postpartum thyroiditis (PPT). Classic PPT is a subclinical condition characterized by the transient occurrence of hyperthyroidism, followed by hypothyroidism beginning (on average) at 19 weeks postpartum and resolving by 1 year (Stagnaro-Green, 2004). This pattern of hyperthyroidism followed by hypothyroidism and then recovery is not universal, however. In a longitudinal study of 640 women, Lucas et al. (2005) found that among the 7.8% who developed PPT, 42% experienced only hypothyroidism without preceding hyperthyroidism. Of those women, 56% ultimately developed persistent hypothyroidism over the next several years (8.1 ± 2.2).

Risk factors for PPT include diabetes mellitus, a personal or family history of autoimmune disease, and a history of thyroid disease or goiter. Women positive for antithyroid peroxidase antibodies (antiTPOAb), a standard prenatal screening assay run early in gestation, are at an especially high risk (Lazarus, 2003). Most women with PPT, however, have no identifiable risk factors.

Evidence-Based Intervention for Thyroid Dysfunction

Clinical diagnosis of hypothyroidism in postpartum women is difficult because many of the symptoms—including fatigue and depressed mood—are nonspecific during this time. Although measuring thyroid hormone levels is not generally recommended for all postpartum women, women who are known to be at high risk or suffering symptoms, including depression or severe fatigue, may benefit from screening. Especially likely to be undiagnosed without screening are women who suffer from subclinical hypothyroidism and whose symptoms, including fatigue, may be mild although still significant compared to euthyroid persons. In the Colorado Thyroid Disease Prevalence Study, significant symptoms were reported by nearly 30% of women with untreated subclinical hypothyroidism, with 18% of the respondents specifically identifying fatigue as a significant complaint (Canaris, Manowitz, Mayor, Ridgway, & Chester, 2000). Again, a telephone call at 2 weeks postpartum for self-report of fatigue may identify women who need to be evaluated for early-onset hypothyroidism; at each subsequent appointment, fatigue should be re-evaluated.

To differentiate between relatively common symptoms of the postpartum period and hypothyroidism, the AACE and others recommend asking postpartum women about symptoms more specifically associated with hypothyroidism (but not the postpartum period), such as dry skin, aches and pains, hoarseness, goiter, fluid retention, forgetfulness, and constipation (AACE, 2002). Screening tests recommended for postpartum women include a sensitive measurement of TSH level, free or total T4 level, and antiTPOAbs. The AACE also recommended that the diagnosis of clinical or subclinical hypothyroidism be considered and assessed in all patients with depression. Currently, there are no studies available that correlate the development of postpartum hypothyroidism with postpartum fatigue.

Women who are diagnosed with overt hypothyroidism are treated with a high-quality levothyroxine. Although management for each woman should be individualized, the usual mean replacement dose is 1.6 mg/kg/day. Women should be reassessed after an interval of at least 6 weeks and treatment titrated as necessary. Treatment of subclinical hypothyroidism is controversial, with reports identifying and denying clear benefits (Chu & Crapo, 2002). None of the studies on the effectiveness of treating subclinical hypothyroidism have been conducted on post-

partum women, however, for whom fatigue might be a more disabling and distressing symptom than for others.

Interactive Effects of Physiological Factors on Postpartum Fatigue

Each of these physiological factors commonly identified as contributing to fatigue—anemia, infection, and thyroid dysfunction—may occur together in the postpartum period and may even synergize. For example, it is known that the inflammatory response can lead to iron deficiency, an occurrence believed to be an evolutionary response that serves to deny bacteria and other microbes access to the high iron levels required for their survival (Weiss, 2005). At the same time, anemia may reduce immune function and increase the risk of infection (CDC, 1998). Likewise, most causes of hypothyroidism, including PPT, are autoimmune in nature, driven by a proinflammatory cytokine immune response. Finally, iron deficiency anemia is associated with lower circulating levels of thyroid hormone, perhaps a result of diminished functioning of the iron-dependent enzyme thyroid peroxidase (TPO) required for the incorporation of iodide into the thyroglobulin molecule (Zimmermann & Kohrle, 2002). Thus, these three conditions have the potential to coexist and augment a woman's fatigue. To date, no studies have looked at any synergistic effects of these conditions in postpartum women.

Linking Postpartum Fatigue and PPD

We and others have suggested that postpartum fatigue is a significant risk factor for PPD (Troy, 2003; Corwin et al., 2005). Moreover, each of the conditions discussed in this article as a potential contributor to fatigue in postpartum women has been linked on its own to the development of PPD. For example, as part of a larger study, we identified postpartum anemia as a significant risk in the development of depression (Corwin, Murray-Kolb, & Beard, 2003). Other studies on the relationship of postpartum anemia and depression have produced mixed results, indicating that more research is required. No studies are available to indicate that women with postpartum infections are at increased risk of developing depression. A limited number of studies, however, link the presence of elevated proinflammatory mediators and PPD (Maes et al., 2000).

The evidence regarding dysfunctional thyroid function postpartum and PPD is also limited. Although postpartum hypothyroidism may contribute to depression, most women with PPD have normal thyroid hormone levels. A study by Lucus, Pizarro, Grenada, Salinas, and Sanmarti (2001) reported results from a sample of 641 women, 11% of whom developed postpartum thyroid dysfunction—defined as overt or subclinical hyperthyroidism—between 1 and 3 months postpartum and/or overt or subclinical hypothyroidism between 3 and 6 months postpartum. In this study, none of the women developed PPD, although the authors did not identify rates of depression in women suffering hypothyroidism alone.

Suggested Clinical Implications

Nurses should consider implementing the following interventions:

- Placing a "red flag" in a woman's prenatal record if she is known in advance to be especially susceptible to conditions associated with postpartum fatigue.
- Encouraging any woman with a particular risk to return for a 2-week postpartum visit for appropriate screening for anemia, infection/inflammation, and thyroid dysfunction.
- Screening all other women for severe fatigue via a 2-week postpartum nurse-initiated telephone call, using the Modified Fatigue Symptom Checklist.
- Asking women about their fatigue.
- Treating anyone found to be anemic with dietary advice, iron therapy, and anticipatory guidance regarding managing fatigue.
- Evaluating all women for infection at the 6-week postpartum visit and evaluating women with fatigue earlier.
- Evaluating thyroid function in women who are at high risk for depression or fatigue.

Clinical Practice Implications

Postpartum anemia, infection/inflammation, and altered thyroid function are decidedly amenable to evidenced-based interventions, provided they are first diagnosed. Healthcare providers, including clinic and office nurses, nurse practitioners, and midwives, are in a position to (a) place a "red flag" in a woman's prenatal record if she is known in advance to be especially susceptible to any of these conditions based on previous medical history, (b) review those red flags

Nurses can institute interventions, such as 2-week postpartum assessment for fatigue and physiological symptoms, and help women get treatment for fatigue.

and any others that develop during delivery before the discharge of a new mother and her infant, (c) encourage any woman with a particular risk to return for a 2-week postpartum visit for appropriate screening, and (d) screen all other women for severe fatigue via a 2-week postpartum telephone call, encouraging women identified as severely fatigued to come in for an appointment as soon as possible. For these recommendations to be implemented, all the stakeholders in women's health (including women's and pediatric healthcare providers and insurance providers) must agree that postpartum fatigue and depression carry emotional and economic expenses that make prevention not only advisable but also cost-effective. Documenting cost effectiveness, in turn, requires well-designed interventions evaluated by evidence-based research. Finally, all new mothers should receive anticipatory guidance on recognizing the signs and symptoms that suggest anemia, infection, or thyroid abnormality and how to prevent and respond to severe postpartum fatigue (Troy, 2003). By these means, clinicians will be better able to assist new mothers in meeting their role demands and may reduce their risk of developing PPD. ✣

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